Abstract—Background: Although cardiac arrest (CA) is commonly cited as a cause of amnesia, patients referred to the authors’ center with a diagnosis of “amnesia” after CA rarely have isolated memory deficits. Objective: To determine whether CA is a cause of pure amnesia and to assess patterns of cognitive deficits after CA. Methods: The authors used cognitive assessment of 11 consecutive patients referred for memory deficits after CA, targeted at deficit domains identified in the literature reviews, and analysis of specific case reports and prospective studies of cognition after CA. Results: The most common pattern of impairment in their patients was a combination of memory and motor deficits with variable executive impairment. No patient had isolated memory impairment. The case reports do not support the claim that isolated amnesia is a residual of CA; most cases of isolated amnesia are caused by subacute episodes of anoxia or excitotoxic injury. The prospective reports identify highly variable patterns of impairment, but isolated amnesia remains rare. Conclusions: Diffuse, sudden ischemic-hypoxic injury caused by cardiac arrest (CA) does not preferentially damage memory systems. Subacute or stepwise hypoxic or excitotoxic injury may cause isolated hippocampal injury and amnesia. The common pattern of impairment in the postacute phase after CA is a combination of memory, subtle motor, and variable executive deficits.

The neurological and cognitive sequelae of cardiac arrest

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In 1998 in the United States, 456,076 deaths were caused by cardiac arrest (CA).1 Of all patients experiencing a CA, between 1.4 and 20% are successfully resuscitated and subsequently discharged from the hospital.2,3 Follow-up studies have shown that one-half of all survivors have cognitive or motor deficits that require a major lifestyle change.4-7 We estimate that there are 12,000 survivors of CA with persistent neurologic deficits each year and a prevalence of ~50,000 impaired survivors.4 Most neurologists encounter these patients during the early phases of coma and confusional states.8 Little is understood about the natural history of recovery or about the precise patterns of more chronic impairment. Many are characterized as having memory deficits,9,10 but whether this is isolated amnesia or co-occurring with other cognitive deficits has never been confirmed by a prospective sequential study. Patients referred to our center for memory impairments have invariably had a variety of deficits not stressed in the literature. This prompted us to review the literature for evidence of isolated memory deficits after CA and to perform a prospective, sequential neuropsychological study on survivors of CA.

Methods. Subjects. Eleven consecutive patients aged <80 years with hypoxic brain injury after out-of-hospital CA were evaluated (table 1). Patients were referred from acute and postacute sources. No patients had previous neurologic or psychiatric disorder or a history of substance abuse.

Tests. Memory was assessed using the Rey Auditory Verbal Learning Test (RAVLT)11 and the Brief Visual Memory Test—Revised (BVMT-R).12 Dependent variables (DVs) were total learned in five trials and delayed recall. Executive function was assessed using Trail Making Test B (TMTB; DV = time to completion), Wisconsin Card Sorting Test14 (WCST; DV = total categories), verbal fluency test (FAS),15 and animal generation.16 Perceptual was assessed using the Benton Judgment of Line Orientation Test,17 the Number Location subtest from the Visual Object and Space Perception Battery,18 and the Benton Visual Discrimination Test.19 Measures of language were selected to assess lexical semantics at the word level: the Boston Naming Test, and Word Comprehension and Word Reading from the Boston Diagnostic Aphasia Exam.20 Motor function was measured using Trail Making Test A (TMTA),21 grooved pegboard,22 and finger tapping23 (using the dominant hand). All tests have published standard values and ranges or thresholds of impairment.

Analysis. A composite Z score was computed when possible for each domain. Scores were transformed into a 5-point scale.
with Z scores $>-1.0$ scored as 0 (no impairment), $Z$ scores $-1.49$ to $-1.0$ as 0.5 (borderline impairment), $Z$ scores $-1.99$ to $-1.5$ as 1.0 (mild impairment), $Z$ scores $-2.49$ to $-2.0$ as 1.5 (moderate impairment), and $Z$ scores $<-2.5$ as 2.0 (severe impairment). The semantic and perceptual tests for which no Z scores were available were scored as 0 (no impairment) or $-2.5$ (impairment) and averaged with the remaining tests of the domain to produce a composite Z score for the combined category. This composite Z score was subsequently transformed using the 5-point scale above.

These scores were entered into a K-means cluster analysis to reveal underlying patterns to the neurologic deficits. This technique serves to identify relatively homogeneous groups based on particular domains of interest. To reduce the number of domains analyzed, we combined lexical-semantic and perceptual domains into one category labeled “cortical deficits,” which were entered into the analysis along with composite memory, executive function, and motor scores.

Literature review. We searched the MEDLINE database from 1966 through 2003 by combining the search terms “hypoxia” or “anoxia” or “cardiac arrest” with the terms “visual perception” or “agnosia” or “amnesia” or “memory disorder” or “ataxia” or “ataxia” or “move-

Results. The results of the neuropsychological testing for our 11 patients are summarized in table 2. On the word comprehension and reading tasks, there was essentially no error. Because of this insensitivity, table 2 only reflects the performance on the Boston Naming Test.

Memory. Ten patients were moderately to severely impaired. The remaining patient had a composite memory Z score of 0.4.

Executive functions. Five patients were severely impaired. One had mild impairment, and two had borderline impairments despite moderate or severe impairment on

Table 1 Patient demographics

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Age/sex</th>
<th>Time to CPR, min</th>
<th>Length of coma, h</th>
<th>Time to testing, mo</th>
<th>Current living situation</th>
<th>Work status</th>
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<tbody>
<tr>
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<td>6</td>
<td>Home, spouse</td>
<td>Disability</td>
</tr>
<tr>
<td>4</td>
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<td>&gt;5</td>
<td>50</td>
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<td>15</td>
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</tr>
<tr>
<td>6</td>
<td>55/F</td>
<td>2</td>
<td>36</td>
<td>10</td>
<td>Home, spouse</td>
<td>Disability</td>
</tr>
<tr>
<td>7</td>
<td>56/M</td>
<td>5</td>
<td>36</td>
<td>18</td>
<td>Home, spouse</td>
<td>Disability</td>
</tr>
<tr>
<td>8</td>
<td>18/M</td>
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<td>30 days</td>
<td>12</td>
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<td>Special Ed</td>
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<tr>
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<td>56</td>
<td>32</td>
<td>Home, spouse</td>
<td>Disability</td>
</tr>
<tr>
<td>11</td>
<td>41/F</td>
<td>6</td>
<td>36</td>
<td>15</td>
<td>Home, spouse</td>
<td>Disability</td>
</tr>
</tbody>
</table>

CPR = cardiopulmonary resuscitation.

Table 2 Neuropsychological testing domains

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Memory (Z score)</th>
<th>Executive (Z score)</th>
<th>Boston Naming (Z score)</th>
<th>Perceptual impairment</th>
<th>Motor (Z score)</th>
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<td>0.9</td>
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<tr>
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<td>0.1</td>
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</tr>
<tr>
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<td>-0.5</td>
<td>0.2</td>
<td>1/3</td>
<td>-2.1</td>
</tr>
<tr>
<td>4</td>
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<td>1/3</td>
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<tr>
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<td>-1.4</td>
<td>0/3</td>
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<td>-1.2</td>
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<td>0/3</td>
<td>-3.8</td>
</tr>
<tr>
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<td>-3.2</td>
<td>-2.8</td>
<td>-1.2</td>
<td>0/3</td>
<td>-2.9</td>
</tr>
<tr>
<td>8</td>
<td>-6.5</td>
<td>-2.9</td>
<td>-2.4</td>
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<tr>
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<td>-3.1</td>
<td>-2.7</td>
<td>1/3</td>
<td>-2.8</td>
</tr>
</tbody>
</table>

Mean Z scores or number of tasks on which performance was abnormal.
two of the three tests. TMTB was the most sensitive task: 7 of 11 had moderate to severe impairment.

**Lexical-semantics.** Only one patient met criteria for moderate to severe impairment. Four patients had moderate to severe impairment on the Boston Naming Test alone, and two had borderline impairment. None of the patients with confrontation naming deficits had perceptually based naming errors or evidence of a loss of semantic knowledge.

**Perception.** Only one patient met criteria for moderate to severe impairment, and one patient had mild impairment. Three patients revealed deficits on one task. No patients had perceptual deficits sufficient to disrupt reading. None of the patients with perceptual impairments had apperceptive agnosia.

**Motor functions.** Nine patients met criteria for moderate to severe impairment. The three tasks—tapping motor speed, dexterity, and motor control—were approximately equally sensitive. These impairments were clinically subtle. No patient had overt tremor, rigidity, choreiform movements, or parkinsonism. One patient (Patient 8) had mild appendicular ataxia of all four limbs. No patient was apraxic on bedside testing.

**Impairment profiles.** Because there were three cognitive domains, we performed a K-means cluster analysis fixing the results to a three-cluster solution. This solution produced significant between-group differences in memory (F[2,8] = 69.64; p < 0.001), executive function (F[2,8] = 44.05; p < 0.001), and naming/perception (F[2,8] = 5.97; p < 0.05). The effect of motor function was not significant (F[2,8] = 2.75; NS). In this group of chronic patients with CA, Cluster 1 represents no impairment. One patient (Patient 1) fit this profile. With a verbal IQ of 123, he had a memory recall score of -0.2 which probably represents memory impairment; however, by the strict criteria of this analysis, his performance was considered normal. Cluster 2 was formed by impairment in memory and motor function with variable performance in executive function (Patients 2 through 6). Three patients (Patients 4 through 6) had borderline to mild impairment of executive function (-1.0 > Z > -2.0), and two had no executive function impairment (Z score between 0 > Z > -1). Cluster 3 comprised patients with significant loading on all domains (Patients 7 through 11).

Although we did not specifically examine the relationship between cognitive impairments and functional status, all 10 patients with memory impairments are receiving disability. Four require a supervised living situation.

**Case reports.** We found 22 case reports with 39 patients who had an uncomplicated CA (see table E-1 on the Neurology Web site). There were two cases with unique presentations: loss of semantic knowledge (Case Report 1) and delayed dystonia (Case Report 5). There were three cases with cognitive deficits in a single domain: amnesia (Case Reports 8 and 22) or visual perceptive problems (Case Report 17). One case had no clear deficits. Nine cases had multiple deficits of moderate severity. Twelve cases had severe deficits. The remaining 12 cases had insufficient clinical or neuropsychological information to categorize. A surprisingly large number of case reports were excluded from this study for not fulfilling inclusion criterion number 5 (isolated CA).

The patients in the moderate injury category had a wide range of signs and symptoms. Coma duration ranged from 15 minutes to 1 week. Some awoke with no initially reported neurologic abnormalities (Case Report 16, Case 6), and others were confused and disoriented (Case Report 13). All patients had deficits in more than one domain. Of the 12 severe cases, 8 reported coma duration, and all were comatose for >24 hours. Two other cases were confirmed to have been in coma, but duration was not provided. All four patients whose emergence from coma was described had a severe confusional state. All patients had deficits in every domain tested, with not all domains tested or discussed in each case report.

**Discussion.** The patients in our sample were referred because of memory complaints, but memory and motor impairment were nearly ubiquitous. Five patients had severe and three had milder executive deficits. Moderate to severe deficits in higher cortical functions, such as language and perception, were uncommon. Cluster analysis suggested three different patterns of deficits: 1) no impairments; 2) global cognitive and motor impairments; and 3) memory plus motor difficulties with variable executive impairment.

Our one patient in Cluster 1 and the small number of case reports with no deficit or only subtle deficits presumably exemplify the largest outcome group of survivors of CA. These patients usually emerge early from coma and demonstrate good recovery quickly, accounting for the plateau of recovery at ~3 months in group studies. Whether the neural injury is entirely transient and reversible or simply too mild to cause lasting or definite deficits is unknown. There may be relative decrements in performance that are obscured by arbitrary cutoffs on tests or functional deficits that are not sensitive to neuropsychological testing. These patients are likely to be under-represented in the literature.

Patients in our Cluster 2 and in several of the case reports reviewed have intermediate outcomes. The relationship between duration of coma and outcome is variable. Our patients all had memory and motor impairments. Executive deficits might have been consistently detected in this group if assessed sooner after emergence from coma and confusion. Patient 6 had a detailed clinical examination 3 months after injury. Executive functioning was very impaired, and she confabulated extensively. When evaluated for this study 10 months after CA, executive function was only borderline impaired, although her performance was likely reduced given her high education (PhD). We propose that these patients have not had permanent widespread cortical damage and may have damage restricted to the selectively vulnerable brain regions. This group of patients may be the most likely to show late (after 3 months) improvement, perhaps making them most appropriate for rehabilitation.

The patients in our Cluster 3 and the patients whom we categorized as severe from case reports have similarly poor outcomes. These patients usually have long periods of coma (>24 hours). In addition to...
memory and executive impairments, language and visuospatial functions are disturbed. This suggests that the injury likely involves cortex and the more vulnerable subcortical and hippocampal regions. Given the severity and range of deficits at several months to years after injury, this population may not benefit from late rehabilitation.

The prevalence of neurologic sequelae in our sample is similar to that reported in group studies. One group examined 68 consecutive patients 1 year after CA. Forty-eight percent of patients had deficits on neuropsychological testing. Although 69% of the patients with deficits had memory difficulties, planning (54%), perception (27%), and language (8%) were also abnormal. In a study of CA patients evaluated during in-patient rehabilitation all had memory impairments, but 60% also had attentional difficulties, and 30% had visual perception problems. In a group of 10 CA survivors selected for persistent neuropsychological deficits, every patient had moderate to severe disturbances in memory function, but 90% also had visuospatial deficits. None of these published studies specifically examined motor or fronto-executive function. Even when distinct profiles of hypoxic injury are specifically probed with a comprehensive neuropsychological battery in stable postacute patients, isolated memory problems have not been demonstrated after CA.

The three case reports (see table E-1 on the Neurology Web site) of isolated deficits after CA do not support the label “isolated.” A patient with simultanagnosia (Case Report 17) had normal performance on the Wechsler Memory Scale, but no other cognitive testing was performed. Two patients with allegedly isolated amnesia had additional deficits clearly described in the reports: apathy, confabulation, and a left hemiparesis in one (Case Report 8), and a co-occurring left frontal lobe infarct in the other (Case Report 22).

This is not to conclude that isolated amnesia cannot occur after CA, but that it is a rare and incompletely documented event. There is an earlier report of six selected patients with isolated amnesia after CA. Overall performance on executive tasks was normal, but individual neuropsychological performances, standardized motor assessments, and clinical histories were not reported. One of these patients even had bibrachial paresis.

Isolated amnesia appears to be more common with other causes of hypoxia. For example, there is an oft-cited group of patients with exhaustive post mortem or imaging studies that confirm that their selective amnesia was caused by isolated hippocampal injury, but none had a CA. One patient had a hypotensive event, and one had seizures. A third patient had several episodes of hypovolemia, hypotension, and a respiratory arrest. The etiologies of the amnesia in three others are unknown but occurred over 3 days and 2 years. We identified seven additional case reports of relatively isolated memory disorder in the setting of neuropsychologically verified normal language, visual, and executive function: one drowning accident (Case 1), one respiratory arrest (Case 3), one hanging, two anesthesia accidents, and three seizures. In the 1996 study of 18 rehabilitation patients, isolated deficits were caused by carbon monoxide poisoning, drowning, or anesthetic accident.

The outcome of all of these etiologies is ultimately anoxia. The basal ganglia, thalamus, Purkinje cells of the cerebellum, the layer III neurons of the cerebral cortex, and the pyramidal neurons of the hippocampus are particularly vulnerable, but specific regions of damage vary depending on the etiology.

CA produces hypoxia and ischemia so abruptly and completely that we postulate that all high-energy neurons may be susceptible with no predefinition to specific vulnerable brain regions. If sufficiently injured, neurons may undergo cell necrosis rather than excitotoxic damage or apoptosis. It has been demonstrated that repeated brief episodes of transient ischemia produce cumulative hippocampal damage that is greater than after a single prolonged episode. If the interval between episodes is 5 minutes, neuronal damage can be restricted to the hippocampus, although it should be noted that repeated exposure can also produce ischemic tolerance. Metabolic injuries that are subacute and prolonged over minutes to hours, such as seizures, gradual hypoxia with maintained perfusion, or prolonged hypovolemia with fluctuating perfusion but maintained ventilation, may predispose to isolated hippocampal damage, whereas pure CA results in more diffuse injury.

Recovery of neurologic deficits after CA is not well understood, but prospective studies indicate that recovery of memory and visuospatial deficits occurs only in the first 3 months, with little recovery afterward. Executive disturbances appear to have the most prolonged course of recovery. Our clinical observation suggests that the executive impairment emerges seamlessly from the early postacute confusional state and may slowly improve over at least 3 to 10 months (e.g., our Patient 6). Although there is no evidence that any intervention is meaningfully effective for true amnesia, there are possible treatments for executive impairment.

A longitudinal study comparing CA patients with a control group with comparable vascular and cardiac risk factors will be required to determine the specificity of patterns of deficits and the relationship of cognitive deficits to functional disability. A separate study directly comparing the consequences of abrupt global hypoxic-ischemic injury with stepwise hypoxic (as with carbon monoxide) or excitotoxic (as with seizures) injury will be necessary to confirm differences in their neuropathologies.

References


